TRANSLATION FROM GERMAN

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World International Property Organization
International Office

[logo]
[WIPO
OMPI]

(43) International Publication Date
March 4, 2004 (3/04/04)

PCT

(10) International Publication Number
WO 2004/018474 A1

(51) International Patent Classification[7]: C07D 487/04, A61 K 31/519, A61P 25/00 // (CO7D) 487/04, 239:00, 231:00

(21) International File Number: PCT/EP2003/008923

(22) International Application Date: August 12, 2003 (8/12/03)

(25) Language of application: German

(26) Language of publication: German

(30) Priority data:
102 38 723.0 August 23, 2002 (8/23/02) DE

(71) Applicant *(for all designated countries, except the US)*: **BAYER HEALTHCARE AG** [DE/DE]; 51368 Leverkusen (DE)

(72) Inventors: and
(75) Inventors/Applicant *(only for the US)*: **Martin HENDRIX** [DE/DE]; Im Geroden 5, 51519 Odenthal (DE). **Frank-Gerhard BÖSS** [DE/DE]; Auf dem Scheidt 29 f, 42115 Wuppertal (DE); **Nils BURKHARDT** [DE/DE]; Unterste Dillenberg 16, 42553 Velbert (DE). **Christian ERB** [DE/DE]; Uhlandstr. 4, 65830 Kriftel (DE). **Adrian TERSTEEGEN** [DE/DE]; Florastr. 32, 42553 Velbert (DE). **Marja VAN KAMPEN** [DE/DE]; Gravenbuchring 79, 63263 Neu-Isenburg (DE)

(74) Joint Attorney: **BAYER HEALTHCARE AG**; Law and Patents, Patents and Licensing, 513681 Leverkusen (DE).

(81) Designated countries *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE,GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated countries *(regional)*: ARIPO Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration according to Rule 4.17:
– with regard to the right of the applicant to apply for and be granted a patent (Rule 4.17ii;; Item) for the following designated countries AE AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:
– with International Search Report

For an explanation of the two-letter code and the other abbreviations, reference is made to the explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of every regular issue of the PCT Gazette.

(54) Title: PHENYL-SUBSTITUTED PYRAZOLOPYRIMIDINES

(57) Abstract: The invention relates to novel phenyl-substituted pyrazolopyrimidines, a method for the production thereof, and their use for producing drugs to improve cognition, concentration, learning and/or memory.

Phenyl-substituted pyrazolopyrimidines

The invention relates to novel phenyl-substituted pyrazlopyrimidines, a method for the production thereof, and their use for producing drugs to improve cognition, concentration, learning and/or memory.

The cellular activation of adenylate or guanylate cyclases effects the cyclization of ATP or GTP to 3',5'-cyclic adenosine monophosphate (cAMP) or 3',5'-cyclic guanosine monophosphate (cGMP). These cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a central role in cellular signal transduction cascades. Both again activate, among others, but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A (PKA) and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA or PKG can, in turn, effect the phosphorylation of a series of cellular effector proteins (e.g., ionic channels, G protein-coupled receptors, structural proteins). In this way, the second messengers cAMP and cGMP can control a wide variety of physiological processes in the most varied organs. But the cyclic nucleotides can also have a direct effect on the effector molecules. Thus, we know for example that cGMP can act directly on ionic channels and can thereby affect cellular ion concentration (survey in: Wei *et al.*, *Prog. Neurobiol.*, **1998**, *56*:37-64). A control mechanism to regulate, in turn, the activity of cAMP and cGMP and hence control these physiological processes are the phosphodiesterases (PDE). PDEs hydrolyze the cyclic monophophates to the inactive monophosphates AMP and GMP. At least 21 PDE genes have meanwhile been described (*Exp. Opin, Investig. Drugs*, **2000**, *9*:1354-3784). These 21 PDE genes can be divided in 11 PDE families on the basis of their sequence homology (for a nomenclature proposal, see http://depts.washington.edu/pde/nomenclature/html). Individual PDE genes within a family are distinguished by letters (e.g., PDE1A and PDE1B). Should differing splice variants occur within a gene, these are then indicated by an additional numeration following these letters (e.g., PDE1A1).

Human PDE9A was cloned and sequenced in 1998. The amino-acid identity to other PDEs is maximally 34% (PDE8A) and minimally 28% (PDE5A). At a Michaelis-Menten constant (K_m value) of 170 nM, PDE9A has a high affinity for cGMP. Beyond that, PDE9A is selective for cGMP (K_m value for cAMP = 230 μM). PDE9A exhibits no cGMP binding domains that could lead one to conclude that cGMP effects allosteric enzyme regulation. Analysis by the Western blot technique has shown that in humans PDE9A is expressed in the testicles, brain, small intestine, skeletal muscles, heart, lungs, thymus, and spleen. The highest expressivity was found to be in the brain, small intestine, heart, and spleen (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25):15559-15564). The gene for human PDE9A lies on chromosome 21q22.3 and contains 21 exons. To date, 4 alternative splice variants of PDE9A have been identified (Guipponi *et al.*, *Hum. Genet.*, **1998**, *103*:386-392). The classic PDE inhibitors do not inhibit human PDE9A.

Thus, IBMX, dipyridamoles, SKF94120, rolipram, and vinpocetine, at concentrations of up to 100 μM, effect no inhibition on isolated enzymes. In the case of zaprinast, the IC_{50} value was demonstrated to be 35 μM (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25): 15559-15564.

Mouse PDE9A was cloned and sequenced by Soderling *et al.* (*J. Biol. Chem.*, **1998**, *273* (19):15553-15558) in 1998. Like the human form, it has high affinity for cGMP, with a K_m of 70 nM. Especially high expressivity was found in the mouse kidney, brain, lung, and heart. In the mouse as well, PDE9A is not inhibited by IBMX in concentrations of less than 200 μM; the IC_{50} value for zaprinast is 29 μM (Soderling *et al.*, (*J. Biol. Chem.*, **1998**, *273* (19):15553-15558). It has been demonstrated that in the rat brain PDE9A is highly expressed in some cerebral regions, including the bulbus olfactorius, hippocampus, cortex, basal ganglia, and basal prosencephalon (Andreeva *et al.*, *J. Neurosci*, **2001**, *21* (22):9068-9076). The hippocampus, cortex, and basal prosencephalon in particular play an important role in learning and memory processes.

As mentioned above, PDE9A is distinguished by especially high affinity for cGMP. That is why PDE9A, unlike PDE2A is already active at even low physiological concentrations (K_m = 10 μM; Martins *et al.*, *J. Biol. Chem.*, **1982**, *257*:1973-1979), PDE5A (K_m = 4 μM; Francis *et al..*, *J. Biol. Chem.*, **1980**, *255*:620-626), PDE6A (K_m = 17 μM; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, *263* (17):8133-8141), and PDE11A (K_m = 0.52 μM; Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, 97 (7):3702-3707. In contrast to PDE2A (Murashima *et al.*, *Biochemistry.*, **1990**, *29*:5285-5292), the catalytic activity of PDE9A is not increased by cGMP, since it exhibits no GAF domains (cGMP binding domains, over which the PDE activity is allosterically enhanced) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, *12*:174-179). PDE9A inhibitors therefore lead to an increase in basal cGMP concentration. This increase in basal cGMP concentration led surprisingly to an improvement of learning and memory performance in the Social Recognition Test.

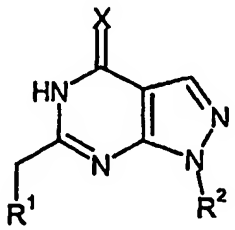
WO 98/40384 discloses pyrazolopyrimidines that excel as PDE1, 2 and 5 inhibitors and can be used for the treatment of cardiovascular and cerebrovascular diseases, as well as urogenital conditions.

CH 396,924, CH 396,925, CH 396,926, CH 396,927, DE 1,147,234, DE 1,149,013, and GB 937,726 describe pyrazolopyrimidines with coronary-dilating action that can be enlisted in the treatment of circulatory disorders of the heart muscle.

US 3,732,225 describes pyrazolopyrimidines that have an anti-inflammatory and blood-sugar lowering effect.

DE 2,408,906 describes styrene pyrazolopyrimidines that can be used as antimicrobial and antiphlogistic agents for the treatment of, e.g., edemas.

The present invention relates to compounds of the formula



(I),

in which

R^1 denotes phenyl that is substituted by 1 to 5 substituents, selected independently of one another from the halogen, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, nitro and C_1-C_6 alkoxy groups,

R^2 denotes pentane-3-yl, C_4-C_6 cycloalkyl,

X denotes oxygen or sulfur,

as well as their salts, solvates and/or solvates of these salts.

The compounds according to the invention are compounds of formula (I) and their salts, solvates and solvates of these salts; the compounds encompassed by formula (I) having the formulas mentioned below and their salts, solvates and solvates of these salts as well as the compounds encompassed by formula (I) mentioned below as exemplary embodiments and their salts, solvates and solvates of these salts, in so far as the compounds encompassed by formula (I) mentioned below are not salts, solvates and solvates of these salts.

The compounds of the invention can, depending on their structure, exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers or diastereomers and their respective mixtures. The stereoisomerical unit components of such mixtures of enantiomers and/or diastereomers can be isolated in otherwise known manner.

Preferred as salts within the scope of the invention are physiologically biocompatible salts of the compounds according to the invention.

Physiologically biocompatible salts of compounds (I) encompass acid addition salts of mineral acids, carboxylic acids and sulfonic acids, e.g., salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalene disulfonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically biocompatible salts of compounds (I) also encompass salts of the usual bases, such as for example and preferably alkali metal salts (e.g., sodium and potassium salts), alkaline earth salts (e.g., calcium and magnesium salts), and ammonium salts derived from ammonia or organic amines with 1 to 16 carbon atoms, such as, for example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, *N*-methylmorpholine, dehydroabietylamine, arginine, lysine, ethylenediamine, and methylpiperidine.

Designated as solvates within the scope of the invention are forms of the compounds that form, in a solid or liquid state, a complex by coordination with solvent molecules. Hydrates are a special form of solvates in which coordination with water occurs.

Moreover, the present invention also encompasses pro-drugs of the compounds according to the invention. The term "pro-drug" includes compounds that can be biologically active or inactive, by themselves, but undergo conversion to compounds of the invention (for example, by metabolic or hydrolytic processes) during their retention time in the body.

Within the scope of the present invention, unless otherwise specified, the substituents have the following meaning:

C_1-C_6 alkoxy stands for a straight-chain or branched alkoxy group with 1 to 6, preferably 1 to 4 and especially preferred 1 to 3, carbon atoms. Preferred examples are methoxy, ethoxy, *n*-propoxy, isopropoxy, *tert*-butoxy, *n*-pentoxy, and *n*-hexoxy.

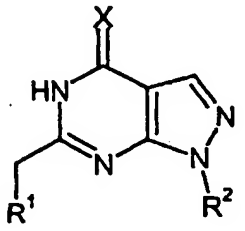
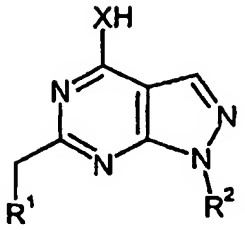
C_1-C_6 alkyl stands for a straight-chain or branched alkyl group with 1 to 6, preferably 1 to 4 and especially preferred 1 to 3, carbon atoms. Preferred examples are methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl, *n*-pentyl, and *n*-hexyl.

C_4-C_6 and C_5-C_6 cycloalkyl stand for saturated or partly unsaturated cycloalkyl groups with 4 to 6, preferably 5 to 6, carbon atoms. Preferred examples are cyclobutyl, cyclopentyl, and cyclohexyl.

Halogen stands for fluorine, chlorine, bromine, and iodine. Preferred are fluorine, chlorine, and bromine; especially preferred are fluorine and chlorine.

When groups in the compounds of the invention are optionally substituted, substitution with up to three like or different substituents is preferred, unless otherwise specified.

The compounds of the invention can also be present as tautomers, as shown for example in the following:

A further embodiment of the invention relates to the compounds of formula (I), in which

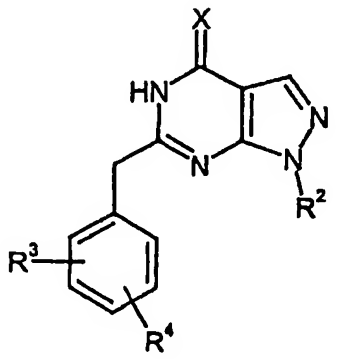
R^1 denotes phenyl that is substituted by 1 to 3 substituents selected independently of one another from the fluorine, chlorine. bromine, C_1-C_4 alkyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, nitro and C_1-C_4 alkoxy groups,

R^2 denotes pentane-3-yl, C_5-C_6 cycloalkyl,

X denotes oxygen or sulfur,

as well as their salts, solvates and/or solvates of these salts.

Another embodiment of the invention relates to compounds of formula



(Ia),

in which

R^3 denotes hydrogen or chlorine,

R^4 denoted fluorine, chlorine, bromine, methyl, trifluoromethyl,

R^2 denotes pentane-3-yl, cyclopentyl

X denotes oxygen and sulfur,

as well as their salts, solvates and/or solvates of these salts.

A further embodiment of the invention relates to compounds of formulas (I) and (Ia),

in which

R^3 denotes hydrogen or chlorine,

R^4 denoted fluorine, chlorine, bromine, methyl, trifluoromethyl,

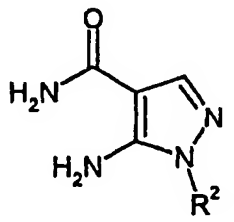
R^2 denotes pentane-3-yl, cyclopentyl

X denotes oxygen,

as well as their salts, solvates and/or solvates of these salts.

Furthermore, a method was found for the preparation of the compounds of the invention, characterized in that either

[A] Compounds of the formula



(II),

in which

R^2 has the above meanings,

by reaction with a compound of the formula

$$R^1\text{-}CH_2\text{-}C(O)\text{-}Z \qquad \text{(IIIa)}$$

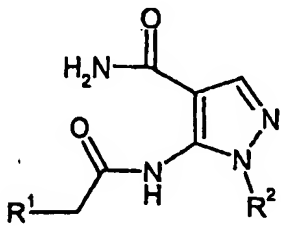
in which

R^1 has the meanings indicated above

and

Z denotes chlorine or bromine,

are converted in an inert solvent and in the presence of a base, first to compounds of the formula

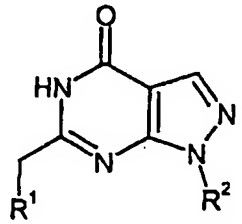


(IV),

in which

R^1 and R^2 have the meanings indicated above,

are then cyclized in an inert solvent in the presence of a base to compounds of the formula



(Ib),

in which

R^1 and R^2 have the meanings indicated above.

or

[B] compounds of formula (II) are reacted under direct cyclization to (Ib) with a compound of the following formula

$$R^1\text{-}CH_2\text{-}C(O)\text{-}OR^5 \quad \text{(IIIb)}$$

in which

R^1 has the meanings indicated above

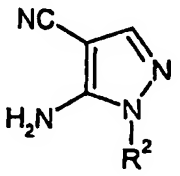
and

R^5 denotes methyl or ethyl,

in an inert solvent and in the presence of a base,

or

[C] compounds of the formula

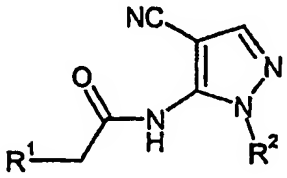


(V),

in which

R^2 has the meanings indicated above,

are converted, first by conversion with a compound of formula (IIIa) in an inert solvent and in the presence of a base, to compounds of the following formula



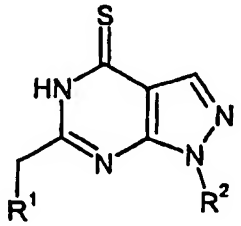
(VI),

in which

R^1 and R^2 have the meanings indicated above,

and these are cyclized, in a second step, in an inert solvent and in the presence of a base and an oxidation agent, to (Ib),

and the compounds of formula (1b) are then optionally converted by reaction with a sulfuration agent, such as, for example, diphosphorous pentasulfide, to the thiono derivative of the following formula



(Ic),

in which

R^1 and R^2 have the meanings indicated above,

and the resulting compounds of formula (I) are converted to their solvates, salts and/or solvates of these salts optionally with the corresponding (i) solvents and/or (ii) bases or acids.

Suitable for the first step of method [A] and method [C] are inert organic solvents that do not change under the reaction conditions. Preferred among these are ether, such as diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether, or toluene or pyridine. It is likewise possible to use mixtures of the solvents mentioned. Especially preferred are tetrahydrofuran, toluene or pyridine.

Suitable as bases are generally alkali hydrides, such as, e.g., sodium hydride or cyclic amines, such as, e.g. piperidine, pyridine, dimethylaminopyridine (DMAP), or C1-C4 alkylamines, as e.g., triethylamine. Preferred are sodium hydride, pyridine and/or dimethylaminopyridine.

The base is generally used in an amount of 1 mol to 4 mol, preferably 1.2 mol to 3 mol, in each instance relative to 1 mol of the compounds of formula (II) or (V).

In a variant, the conversion is effected in pyridine, to which a catalytic amount of DMAP is added. Optionally, toluene can also be added.

The reaction temperature can generally be varied over a relatively large range. In general, the reaction is carried out within a range of –20°C to +200°C, preferably 0°C to +100°C.

Suitable as solvents for the cyclization in the second step of the methods [A] and [C] are the usual organic solvents. These preferably include alcohols, such as methanol, ethanol, propanol, isopropanol, *n*-butanol or *tert*-butanol, or ethers, such as tetrahydrofuran or dioxane, or dimethylformamide or dimethylsulfoxide. Especially preferred for use are alcohols like methanol, ethanol, propanol, ispropanol or *tert*-butanol. It is also possible to use mixtures of the said solvents.

Suitable as bases for the cyclization in the second step of the methods [A] and [C] are the usual inorganic bases. These preferably include alkali hydroxides or alkaline earth hydroxides such as, e.g., sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali carbonates such as sodium carbonate or potassium carbonate or sodium hydrogen carbonate, or alkali alcoholates such as sodium methanolate, sodium ethanolate, potassium methanolate, potassium ethanolate or potassium *tert*-butanolate. Especially preferred are potassium carbonate, sodium hydroxide, and potassium *tert*-butanolate.

For carrying out the cyclization, the base is generally used in an amount of 2 mol to 6 mol, preferably 3 mol to 5 mol, in each instance relative to 1 mol of the compounds of formula (IV) or (VI).

Suitable as oxidizing agents for the cyclization in the second step of the method [C] are, for example, hydrogen peroxide or sodium borate. Hydrogen peroxide is preferred.

The cyclization in methods [A], [B], and [C] is generally effected within a temperature range of 0°C to +160°C, preferably at the boiling temperature of the particular solvent used.

The cyclization is generally effected under normal pressure. However, it is also possible to carry out the method at excess pressure or reduced pressure (for example, within a range of from 0.5 to 5 bar).

Suitable as solvents for method [B] are the alcohols listed above for the second step of methods [A] and [C], with ethanol being preferred.

Suitable as bases for method [B] are alkali hydrides, such as, e.g., sodium hydride or potassium hydride, or alkali alcoholates, such as, e.g., sodium methanolate, sodium ethanolate, sodium isopropylate or potassium *tert*-butylate. Sodium hydride is preferred.

The base is used in an amount of 2 mol to 8 mol, preferably 3 mol to 6 mol, in each instance relative to 1 mol of the compounds of formula (II).

The compounds of formula (II) are known or can be prepared, for example, by first condensing ethoxy methylene malonic acid dinitrile with hydrazine derivatives of the formula

$$R^2\text{-NH-NH}_2 \quad \text{(VII)},$$

in which

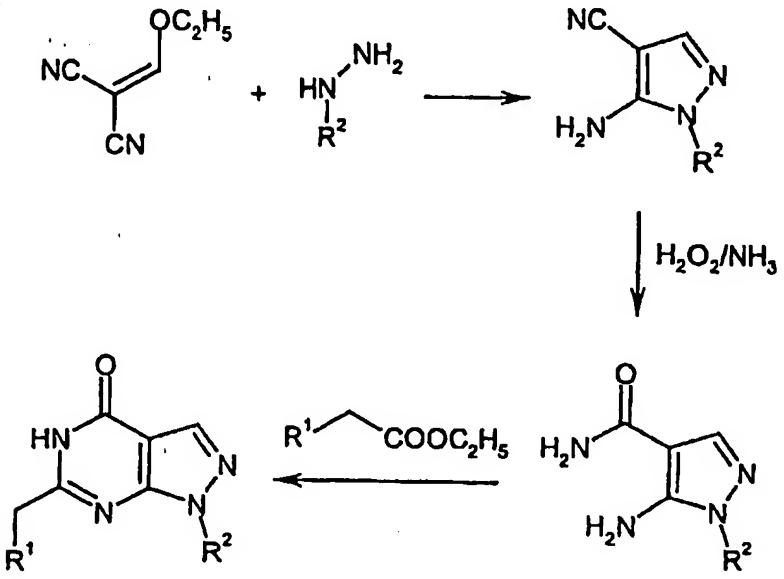
R^2 has the meanings indicated above,

in an inert solvent to the pyrazol nitriles of formula (V) and then converting these with one of the oxidizing agents listed above, preferably hydrogen peroxide, in the presence of ammonia [cf., e.g., A. Miyashita *et al.*, *Heterocycles*, **1990**, *31*:1309 ff].

The compounds of formula (IIIa), (IIIb), and (VII) are commercially available, known from the literature or can be prepared analogously to methods known from the literature.

The process according to the invention can be illustrated for example by the following formula diagram:

Diagram



Other processes for the preparation of pyrazolo[3,4-d]pyrimidine-4-ones are known and can likewise be used for the synthesis of the compounds of the invention (cf, for example: P. Scmidt *et al.*, *Helvetica Chimica Acta,* **1962**, *189*:1620 ff).

The compounds of the invention exhibit an unanticipated, valuable pharmacological and pharmacokinetic spectrum of action.

They are therefore suitable for use as drugs for the treatment and/or prophylaxis of human and animal diseases.

The term "treatment" within the scope of the present invention includes prophylaxis.

It was surprisingly found that selective PDE9A inhibitors are suitable for the preparation of drugs to improve cognition, concentration, learning or memory.

The compounds of the invention can, on the basis of their pharmacological properties alone or in combination with other drugs, be used to improve cognition, concentration, learning and/or memory.

A PDE9A inhibitor, in the sense of the invention, is a compound that inhibits human PDE9A, with an IC_{50} value of less than 10 μM, preferably less than 1 μM, under the conditions indicated below.

A selective PDE9A inhibitor, in the sense of the invention, is a compound that, under the conditions indicated below, inhibits human PDE9A more strongly than human PDE1C, PDE2A, PDE3B, PDE4B, PDE5A, PDE7B, PDE8A, PDE10A, and PDE11. Preferred is an IC_{50} ratio of (PDE9A) to IC_{50} (PDE1C, PDE2A, PDE3B, PDE4B, PDE5A, PDE7B and PDE10A) of less than 0.2.

The selective PDE9A inhibitors are especially suitable for the improvement of cognition, concentration, learning or memory following cognitive disorders, such as occur, in particular, in situations/diseases/syndromes of "mild cognitive impairment," age-related learning and memory disturbances, age-related loss of memory, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post-stroke dementia), post-traumatic dementia, general concentration disturbances, concentration disturbances in children with learning and memory problems, Alzheimer's disease, dementia with Lewy bodies, dementia with frontal-lobe degeneration including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jakob disease, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

The *in vitro* effect of the compounds of the invention can be demonstrated by the following biological assays:

PDE inhibition

Recombinant PDE1C (GenBank/EMBL Accession Number: NM_005020, Loughney *et al., J. Biol. Chem.,* **1996**, *271,* 796-806), PDE2A (GenBank/EMBL Accession Number:NM_002599, Rosman *et al., Gene,* **1997**, *191:*89-95), PDE3B (GenBank/EMBL Accession Number: NM_000922, Miki *et al., Genomics,* **1996**, *36:*476-485), PDE4B (GenBank/EMBL Accession Number: NM_002600, Obernolte *et al., Gene,* **1993**, *129:*239-247), PDE5A (GenBank/EMBL Accession Number: NM_001083, Loughney *et al.,Gene.,* **1998**, *216:*139-147), PDE7B (GenBank/EMBL Accession Number: NM_018945, Hetman *et al., Proc. Natl. Acad. Sci. USA,* **2000**, *97:*472-476), PDE8A (GenBank/EMBL Accession Number: AF_056490, Fisher *et al., Biochem. Biophys. Res. Commun.,* **1998**, *246:*570-577), PDE9A (Fisher *et al., J. Biol. Chem.,* **1998**, *273* (25):15559-15564), PDE10A (GenBank/EMBL Accession Number: NM_06661, Fujishige *et al. , J. Biol. Chem.,* **1999**, *274:*18438-45), PDE11A (GenBank/EMBL Accession Number: NM_016953, Fawcett *et al., Proc. Natl. Acad. Sci.,* **2000**, *97:*3702-3707), were expressed in Sf9 cells with the aid of pFASTBAC Baculovirus Expression System (GibcoBRL).

The test substances are dissolved in 100% DMSO to determine their *in vitro* effect on PDE9A and serially diluted. Typically, dilution series of 200 µM to 1.6 µM are prepared (resulting end

concentrations in the test: 4 µM to 0.032 µM). Each time 2-µL portions of the diluted solutions of the substance are poured into the wells of the microtiter plates (Isoplates, Wallac Inc., Atlanta, GA). Then 50 µL of a dilution of the PDE9A preparation described above is added. The dilution of the PDE9A preparation is selected in such a way that during subsequent incubation less than 70% of the substrate is converted (typical dilution: 1:10,000; dilution buffer: 50 mM tris/HCl, pH of 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA, 0.2% BSA). The substrate, [8-^{3}H] guanosine 3',5'-cyclic phosphate (1 µCi/µL; Amersham Pharmacia Biotech, Piscataway, N.J.) is diluted with assay buffer (50 mM TRIS/HCl, pH of 7.5, 8.3 mM $MgCl_2$, 1.7 mM EDTA) to a concentration of 0.0005 µCi/µL. The enzyme reaction is finally started by the addition of 50 µL (0.025 µCi) of the diluted substrate. The test batches are incubated for 60 min at room temperature and the reaction stopped by the addition of 25 µL of a PDE9A inhibitor (e.g., the inhibitor of preparation example 1, 10 µM final concentration) dissolved in assay buffer. Immediately afterwards, 25 µL of a suspension with 18 mg/mL of yttrium scintillation proximity beads (Amersham Pharmacia Biotech, Piscataway, NJ) is added. The microtiter plates are sealed with a film and allowed to stand for 60 min at room temperature. Whereupon the plates are measured in a Microbeta scintillation counter (Wallac Inc., Atlanta, GA) for 30 s per well. The IC_{50} values are determined against the percentage inhibition on the graphic plot of the substance concentration.

The *in vitro* effect of test substances on recomnbinant PDE3B. PDE4B, PDE7B, PDE8A, PDE10A and PDE11A was determined according to the test protocol described above for PDE9A, with the following adjustments. The substrate used was [5',8'-^{3}H] adenosine 3',5'-cyclic phosphate (1 µCi/µL; Amersham Pharmacia Biotech, Piscataway, NJ). The addition of an initiator solution to stop the reaction is not necessary. Instead, the incubation of substrate and PDE was immediately followed by the addition of the yttrium scintillation proximity beads, as described above, which stopped the reaction. To determine a corresponding effect on recombinant PDE1C, PDE2A and PDE5A, the protocol was additionally adjusted as follows: In the case of PDE1C, calmodulin 10^{-7} M and $CaCl_2$ 3 mM were added to the reaction batch. PDE2A was stimulated in the test by the addition of cGMP 1 µM and tested with a BSA concentration of 0.01%. For PDE1C and PDE2A the substrate used was [5',8'-^{3}H] adenosine 3',5'-cyclic phosphate (1 µCi/µL, from Amersham Pharmacia Biotech, Piscataway, NJ) and for PDE5A the substrate was [8-^{3}H] guanosine 3',5'-cyclic phosphate (1 µCi/µL), from Amersham Pharmacia Biotech, Piscataway, NJ).

The PDE9A-inhibiting effect of the compounds of the invention can be shown by the following examples:

Table 1

Example	IC_{50} [nM]
1	20
2	30
4	30
10	64
13	30

Increase in the intracellular neuronal cGMP concentration in cell cultures

PDE9A inhibitors increase the intracellular neuronal cGMP in cultured primary cortical neurons.

Rat embryos were decapitated (on embryo days E17-E19) and the heads transferred to preparation dishes filled with preparation medium (DMEM, penicillin/streptomycin, both from Gibco). The scalp and skull cap were removed and the exposed brains were transferred to another Petri dish containing preparation medium. Using a binocular microscope and two forceps, the cerebral cortex was isolated and cooled on ice at 4°C. This preparation and the separation of the cortical neurons were then carried out using the papain kit (Worthington Biochemical Corporation, Lakewood, New Jersey 08701, U.S.A.) according to a standard protocol (Huettner *et al., J. Neurosci.*, **1986**, *6*:3044-3060). The mechanically isolated cortical neurons were then cultured under standard conditions (37°C, 5% CO_2) in batches of 150,000 cells/well in 200 µL neurobasal medium/hole (neurobasal; B27 supplement; 2 mM L-glutamine; in the presence of penicillin/streptomycin; all agents obtainable from Gibco) for 7 days in 96 perforated plates (pretreated with 100 µg/mL poly-D-lysine for 30 min). After 7 days the medium was removed and the cells were washed with HBSS buffer (Hank's balanced salt solution from Gibco/BRL). Then, 100 µL of the compound according to the invention, dissolved in HBSS buffer (with prior dissolution in 100% DMSO: 10 mM), was poured on the cells. Whereupon 100 µL HBSS buffer was added once more, so that the final concentration of the compounds of the invention ranges, for example, from 20 nM to 10 µM and incubates at 37°C for 20 min. The test buffer was then completely removed. This is followed by lysis of the cells in 200 µL of lysis buffer (cGMP kit, code RPN 226, from Amersham Pharmacia Biotech.) and the cGMP concentration measured according to the specifications of the manufacturer. All measurements were carried out in triplicate. The statistical analysis was effected with Prism software, version 2.0 (GraphPas Software Inc., San Diego, CA, U.S.A.).

Incubation of the primary neurons with the compounds of the invention resulted in an increase of cGMP content.

Long-term potentiation

Long-term potentiation is regarded as a cellular correlate for learning and memory processes. The following method can be used to determine whether PDE9 inhibition has an effect on long-term potentiation:

Rat hippocampi are placed at an angle of approximately 70 degrees in relation to the cutting blade (chopper). The hippocampus is cut in slices 400 µm apart. The sections are removed from the blade by means of a very soft, highly wetted (marten hair) brush and transferred to a glass vessel with carbogenated cooled nutrient solution (124 mM NaCl, 4.9 mM KCl, 1.3 mM $MgSO_4$ x 7 H_20, 2.5 mM anhydrous $CaCl_2$, 1.2 mM KH_2PO_4, 25.6 mM $NaHCO_3$, 10 mM glucose, pH of 7.4). During the measurement, the sections are in a constant-temperature chamber under a liquid level 1-3 mm deep. The flow rate is 2.5 mL/min. Pregassing is effected under slight overpressure (about 1 atm) as well as through a microneedle in the prechamber. The cutting chamber is connected to the prechamber in such a way that minicirculation can be maintained. The carbogen streaming through the microneedle is used to spur the minicirculation. The freshly prepared hippocampal sections are adapted in the cutting chamber for at least 1 hour at 33°C.

The stimulation intensity is selected in such a way that the focal excitatory postsynaptic potentials (fEPSP) amount to 30% of the maximum excitatory postsynaptic potential (EPSP). Using a monopolar stimulating electrode made of enameled stainless steel and a constant-current biphasic stimulus generator (AM systems 2100), the Schaffer collaterals are locally stimulated (voltage: 1-5 V, pulse duration of one polarity: 0.1 ms, total pulse: 0.2 ms). The excitatory postsynaptic potentials (fEPSP) in the stratum radiatum are recorded by means of glass electrodes (borosilicate glass with filament, 1-5 MΩ, diameter: 1.5 mm, major diameter of thread: 3-20 µm), filled with normal nutrient solution. The field potentials are measured against a chlorinated silver reference electrode located at the edge of the cutting chamber, by means of a d.c. amplifier. The field potentials are filtered through a low-pass filter (5 kHz). The slope of the fEPSPs (fEPSP slope) is determined for the statistical analyses of the experiments. The recording, analysis and control of the experiment are assured by a software program (PWIN), which had been developed in the Neurophysiology Department. Averaging the fEPSP slope data at the indicated times and plotting of the diagrams was accomplished by means of the EXCEL software, with a corresponding macro automating the recording of the data.

Superfusion of the hippocampal sections with a 10 µM solution of the compounds of the invention results in a significant increase in long-term potentiation.

Social recognition test

The social recognition test is a learning and memory test. It measures the ability of rats to distinguish between known and unknown members of the species. That is why this test is suitable for testing the improvement in learning and memory produced by the compounds of the invention.

Adult rats kept in groups are brought individually into test cages 30 min before starting the test. Four minutes before the start of the test, the test animal is placed in an observation box. Following this adaptation time, a juvenile animal is placed with the test animal and for 2 minutes the absolute time is measured during which the adult animal inspects the young one (trial 1). All behavior patterns clearly directed at the young animal, during which the older animal remains at a distance of at most 1 cm from the young animal, are measured, i.e., anogenital inspection and chasing as well as grooming. The juvenile rat is then removed, the adult animal treated with one of the compounds or vehicle of the invention and subsequently returned to its home cage. After a retention time of 24 hours, the test is repeated (trial 2). A decrease in social interaction time, compared to trial 1, indicates that the adult rat remembered the young animal.

Right after trial 1, the adult animals are injected intraperitoneally with either the vehicle (10% ethanol, 20% Solutol, and 70% physiological saline solution) or with 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg or 3.0 mg/kg of the compound of the invention, dissolved in 10% ethanol, 20% solutol, and 70% physiological saline solution. The rats treated with the vehicle exhibited no reduction in social interaction time in trial 2 compared to trial 1. They had consequently forgotten that they had once had contact with the young rat. Surprisingly, the social interaction time in the second pass after treatment with the compounds of the invention was significantly reduced, compared to the vehicle-treated animals. This means that the rats treated with the substance remembered the juvenile animal and that therefore the compounds of the invention had an improving effect on learning and memory.

Another subject of the present invention is a method for the treatment and/or prophylaxis of diseases, especially the diseases mentioned above, with the use of an effective amount of the compounds of the invention.

Another subject of the present invention are drugs containing at least one compound of the invention and at least one or more other active substances, especially for the treatment and/or prophylaxis of the above-mentioned diseases.

The compounds of the invention can act systemically and/or locally. To that end, they can be administered in suitable manner, such as, e.g., orally, parenterally, pulmonarily, nasally, sublingually, lingually, buccally, rectally, cutaneously, transdermally, conjunctivally, aurally or as an implant or stent.

For these routes of administration the compounds of the invention can be administered in suitable dosage forms.

For oral administration, suitable dosage forms releasing the compounds of the invention which are fast-acting and/or modified according to the state of the art and contain the compounds of the invention in crystalline and/or amorphous and/or dissolved form, such as, e.g., tablets (uncoated or coated tablets with, for example, gastric-juice resistant [enteric-coated] or delayed-solubilization or insoluble coatings that control the release of the compound of the invention), tablets which disintegrate rapidly in the oral cavity or films/wafers, films/freeze-dried forms, capsules (for example, hard or soft gelatin capsules), dragées, granulates, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can occur by by-passing an absorption step (e.g., intravenously, intra-arterially, intracardially, intraspinally or intralumbarly) or including absorption (e.g., intramuscularly, subcutaneously, intradermally, percutaneously or intraperitoneally). Also suitable for parenteral administration are also dosage forms, such as forms for injection and infusion in the form of solutions, suspensions, emulsions, freeze-dried preparations or sterile powders.

As to the other routes of administration, suitable are inhalation drug-dosage forms (among them, powder inhalations, nebulizers), nose drops, nasal solutions, nasal sprays; lingual, sublingual or buccal tablets, films/wafers or capsules, suppositories, ear drops, eye drops, vaginal capsules, aqueous suspensions (lotions, mixtures to be shaken), lipophilic suspensions, ointments, creams, transdermal therapeutic systems (such as, for example, plasters), milk, pastes, foams, dusting powders, implants or stents.

The compounds of the invention can be converted to the dosage forms indicated. This can be accomplished by mixing with inert, nontoxic, pharmaceutically suitable adjuvants in otherwise known manner. Such adjuvants include carrier substances (for example, microcystalline cellulose, lactose, mannitol), solvents (e.g., liquid polyethyelene glycols), emulsifiers and dispersants or wetting agents [humectants] (for example, sodium dodecyl sulfate, polyoxysorbitan oleate), binders (for example, polyvinyl pyrrolidone), synthetic and natural polymers (for example, albumin), stabilizers (e.g., antioxidants such as, for example, ascorbic

acid), dyes (e.g., inorganic pigments such as, for example, iron oxides), and taste and/or odor corrigents.

Another subject of the present invention are drugs that contain at least one compound of the invention, usually together with one or more inert, nontoxic, pharmaceutically suitable adjuvants, as well as their use for the aforementioned purposes.

In general, it has proven beneficial in parenteral administration to administer daily amounts of about 0.001 to 10 mg/kg body weight for achieving effective results. For oral administration, the daily amount is about 0.005 to 3 mg/kg body weight.

However, it may optionally be necessary to deviate from the amounts mentioned, and specifically depending on body weight, route of administration, individual response to the active substance, type of preparation and time or interval at which administration occurs. Thus, it may be sufficient to make do with less than the above-mentioned minimum amount in some cases, whereas in others the upper limit indicated above may have to be exceeded. If larger amounts are administered, it may be desirable to subdivide these in several individual doses during the day.

Unless otherwise indicated, the percentages in the following tests and examples are percent by weight, and parts are parts by weight. Solvent ratios, dilution ratios, and concentration data of liquid/liquid solutions always refer to volume.

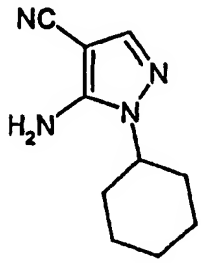
Abbreviations used:

DCI	direct chemical ionization (in MS)
DCM	dichloromethane
DMSO	dimethyl sulfoxide
equiv.	equivalent(s)
ESI	electrospray ionization (in MS)
HPLC	high-pressure, high-performance liquid chromatography
mp.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance
of th.	of theoretical (in relation to yield)
TRIS	2-amino-2-(hydroxymethyl)-1,3-propanediol

Parent compounds:

Example 1A

5-Amino-1-cyclohexyl-1H-pyrazole-4-carbonitrile

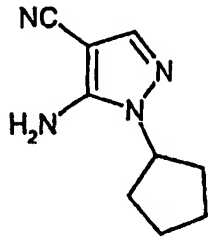


A solution of cyclohexylhydrazine hydrochloride (3 g, 19.9 mmol) in 36 mL ethanol is reacted at room temperature first with ethoxymethylene malonic dinitrile (2.43 g, 19.9 mmol) and then with 8 mL triethlamine. The mixture is refluxed for 20 min and then cooled. The solvent is drawn off in the rotary evaporator and the residue absorbed in DCM, washed with aqueous sodium hydrogen carbonate solution, dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product is chromatographed on silica gel (mobile solvent: dichloromethane/methanol 0-10%).

Yield: 1.95 g (51% of th.)
MS (DCI): m/z = 191 $(M+H)^+$
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 7.5 (s, 1H), 6.5 (s, 2H), 4.0 (m, 1H), 1.95-1.05 (m, 10H) ppm.

Example 2A

5-Amino-1-(1-cyclopentyl)-1H-pyrazole-4-carbonitrile

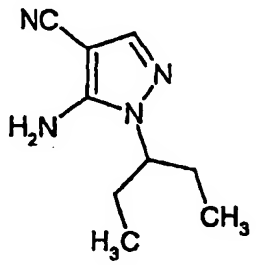


Preparation is analogous to the direction for Example 1A.
MS (ESI): m/z = 177 $(M+H)^+$

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.5 (s, 1H), 4.45 (wide, s, 2H), 4.35 (m, 1H), 2.2-1.55 (m, 6H) ppm.

Example 3A

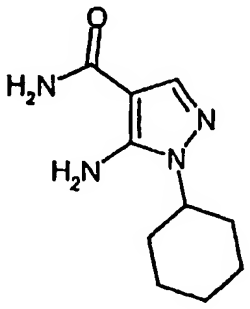
5-Amino-1-(1-ethylpropyl)-1H-pyrazole-carbonitrile



Preparation is analogous to the direction for Example 1A.
MS (ESI): m/z = 179 $(M+H)^+$
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.55 (s, 1H), 6.45 (s, 2H), 4.0 (m, 1H), 1.8-1.55 (m, 4H), 0.65 (t, 6H) ppm.

Example 4A

5-Amino-1-cyclohexyl-1H-pyrazole-carboxamide

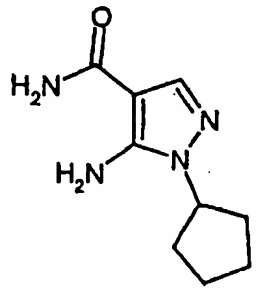


A solution of 5-amino-1-cyclohexyl-1H-pyrazole-4-carbonitrile (1.86 g, 9.81 mmol) in a mixture of 73 mL ethanol and 90 mL concentrated aqueous ammonia solution is reacted at room temperature with 18 mL 30% hydrogen peroxide solution and stirred for 1 h at room temperature. Then the nonaqueous solvents are drawn off in the rotary evaporator. The product precipitates from the remaining mixture as a solid, which is drawn off by suction, washed with a little water, and dried in a high vacuum.
Yield: 1.77 g (86% of th.)
MS (DCI): m/z = 209 $(M+H)^+$
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.6 (s, 1H), 7.3-6.4 (wide, 2H), 6.1 (s, 2H), 3.95 (m, 1H),

1.95-1.05
(m, 10H) ppm.

Example 5A

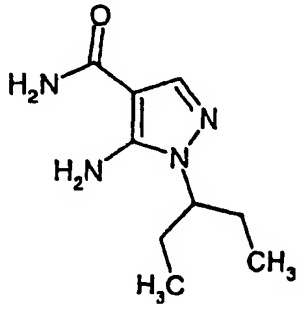
5-Amino-1-cyclopentyl-1H-pyrazole-4-carboxamide



Preparation is analogous to the direction for Example 4A.
MS (ESI): m/z = 195 $(M+H)^+$
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 7.5 (s, 1H), 5.6-4.8 (wide, 4H), 4.35 (m, 1H), 2.2-1.55 (m, 8H) ppm.

Example 6A

5-Amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide

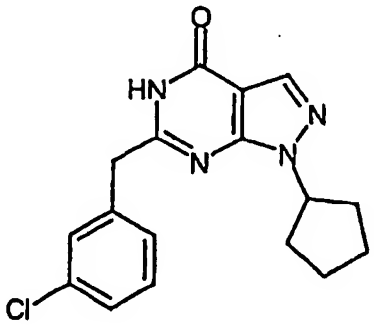


Preparation is analogous to the direction for Example 4A.
MS (ESI): m/z = 197 $(M+H)^+$
^{1}H-NMR (300 MHz, DMSO-d_6): δ =7.65 (s, 1H), 6.9 (wide s, 2H), 6.1 (s, 2H), 3.9 (m, 1H), 1.85-1.6 (m, 4H), 0.7 (t, 6H) ppm.

Exemplary embodiments:

Example 1

6-(3-Chlorobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Under argon gas, 180 mg (0.91 mmol) of 5-amino-1-cyclopentyl-1H-pyrzole-4-carboxamide and 575 mg (2.72 mmol; 3 equiv.) of (3-chlorophenyl acetic acid ethyl ester are prepared in 3.5 mL absolute ethanol. At 0°C, 127 mg of sodium hydride (60% dispersion in mineral oil; 3.18 mmol; 3.5 equiv.) is slowly added in an argon countercurrent. The resulting mixture is slowly heated and stirred for 18 h under reflux. For reprocessing, 50 mL of water is added and the mixture is repeatedly extracted with ethyl acetate. The combined organic phases are dried and evaporated under vacuum. The crude material is purified by preparative HPLC.

Yield: 244 mg (81% of th.).

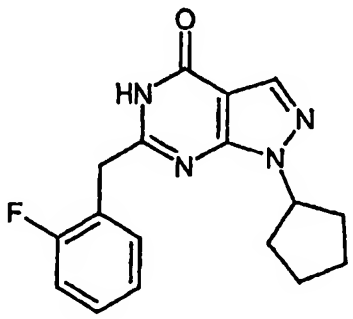
MS (ESI):m/z = 329 $(M+H)^+$

mp.: 159°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.3 (s, 1H), 8.0 (s, 1H), 7.5-7.2 (m, 4H), 5.05 (m, 1H), 3.95 (s, 2H), 2.2-1.5 (m, 8H) ppm.

Example 2

6-(2-fluorobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 100 mg (0.5 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 260 mg (1.51 mmol) of (2-fluorophenyl)-methyl acetate.

Yield: 100 mg (63% of th.)

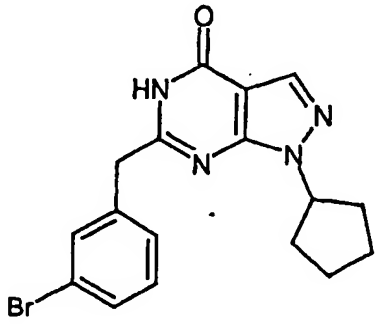
MS (DCI): m/z = 313 $(M+H)^+$

mp.: 180°C

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.25 (s, 1H), 8.0 (s, 1H), 7.4-7.3 (m, 2H), 7.2-7.1 (m, 2H), 4.95 (m, 1H), 4.05 (s, 2H), 2.05-1.55 (m, 8H) ppm.

Example 3

6-(3-Bromobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 80 mg (0.4 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 277 mg (1.21 mmol) of (3-bromophenyl)-methyl acetate.

Yield: 93 mg (62% of th.)

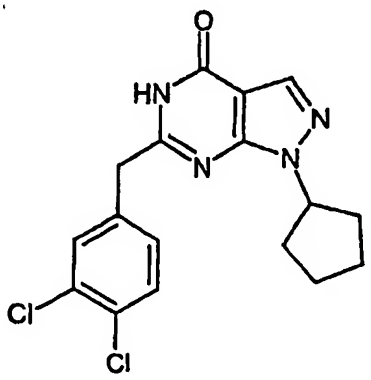
MS (ESI): m/z = 373 $(M+H)^+$

mp.: 159°C

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.2 (s, 1H), 8.0 (s, 1H), 7.6 (s, 1H), 7.5-7.35 (m, 3H), 5.05 (m, 1H), 4.0 (s, 2H), 2.1-1.6 (m, 8H) ppm.

Example 4

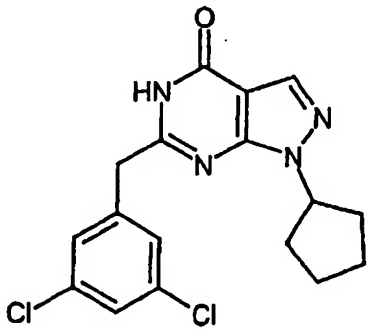
6-(3,4-Dichlorobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 75 mg (0.38 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 254 mg (1.14 mmol) of (3,4-dichlorophenyl)-methyl acetate.
Yield: 94 mg (68% of th.)
MS (ESI): m/z = 363 $(M+H)^+$
mp.: 198°C
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.2 (s, 1H), 8.0 (s, 1H), 7.65 (d, 1H), J = 1 Hz), 7.55 (d, 1H, J = 7.5 Hz), 7.3 (dd, 1H, J = 7.5 Hz, 1 Hz), 5.05 (m, 1H), 4.0 (s, 2H). 2.1-1.6 (m, 8H) ppm.

Example 5

6-(3,5-Dichlorobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one

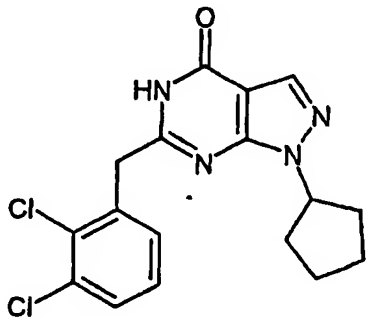


Analogously to Example 1, the product is obtained starting from 150 mg (0.76 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 507 mg (2.27 mmol) of (3,5-dichlorophenyl)-methyl acetate.

Yield: 159 mg (58% of th.)
MS (ESI): m/z = 363 $(M+H)^+$
mp.: 177°C
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.25 (s, 1H), 8.0 (s, 1H), 7.55 (t, 1H), J = 1 Hz), 7.45 (d, 2H, J = 1 Hz), 5.05 (m, 1H), 4.0 (s. 2H), 2.2-1.5 (m, 8H) ppm.

Example 6

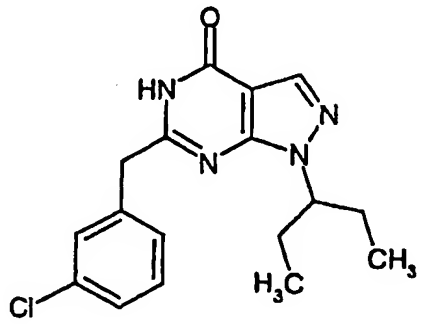
6-(2,3-Dichlorobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 150 mg (0.76 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 406 mg (1.82 mmol) of (2,3-dichlorophenyl)-methyl acetate.
Yield: 114 mg (41% of th.)
MS (ESI): m/z = 363 $(M+H)^+$
mp.: 181°C
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.35 (s, 1H), 8.0 (s, 1H), 7.6 (m, 1H), 7.4-7.3 (m, 2H), 4.9 (m, 1H), 4.2 (s, 2H), 2.1-1.5 (m, 8H) ppm.

Example 7

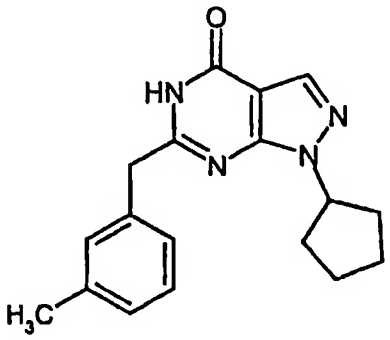
6-(3-Chlorobenzyl)-1-ethylpropyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 150 mg (0.76 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 484 mg (2.29 mmol) of (3-chlorophenyl)-ethyl acetate.
Yield: 210 mg (83% of th.)
MS (ESI): m/z = 331 $(M+H)^+$
mp.: 138°C
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.3 (s, 1H), 8.0 (s, 1H), 7.45-7.25 (m, 4H), 4.45 (m, 1H), 4.0 (s, 2H), 2.0-1.7 (m, 4H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 8

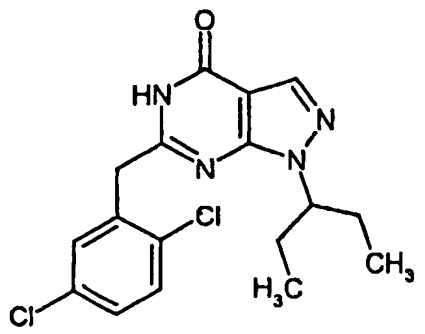
6-(3-Methylbenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 200 mg (1.01 mmol) of 5-amino-1-(1-cyclopentyl)-1H-pyrazole-4-carboxamide and 550 mg (3.03 mmol) of (3-methylphenyl)-ethyl acetate.
Yield: 222 mg (71% of th.)
MS (ESI): m/z = 309 $(M+H)^+$
mp.: 152°C
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.2 (s, 1H), 8.0 (s, 1H), 7.3-7.0 (m, 4H), 5.1 (m, 1H), 3.95 (s, 2H), 2.3 (s, 3H), 2.2-1.55 (m, 8H) ppm.

Example 9

6-(2,5-Dichlorobenzyl)-1-(1-ethylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 806 mg (3.5 mmol) of (2,5-dichlorophenyl)-methyl acetate.

Yield: 51 mg (14% of th.)

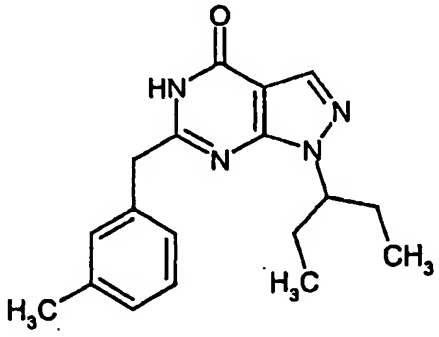
MS (ESI): m/z = 365 $(M+H)^+$

mp.: 134°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.3 (s, 1H), 8.0 (s, 1H), 7.55-7.35 (m, 3H), 4.2 (m, 1H), 4.15 (s, 2H),1.9-1.65 (m, 4H), 0.55 (t, 6H, J = 7.5 Hz)) ppm.

Example 10

6-(3-Methylbenzyl)-1-(1-ethylpropyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 200 mg (1.0 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 534 mg (3.0 mmol) of (3-methylphenyl)-ethyl acetate.

Yield: 187 mg (60% of th.)

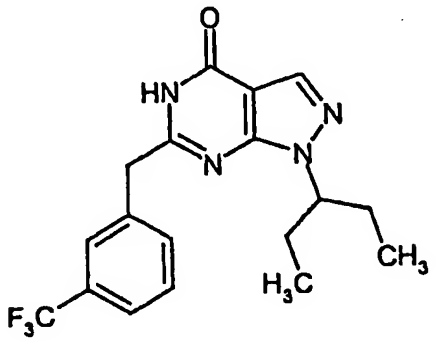
MS (ESI): m/z = 311 $(M+H)^+$

mp.: 128°C

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 12.25 (s, 1H), 8.0 (s, 1H), 7.25-7.0 (m, 4H), 4.5 (m, 1H), 3.95 (s, 2H), 2.25 (s, 3H), 2.0-1.7 (m, 4H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 11

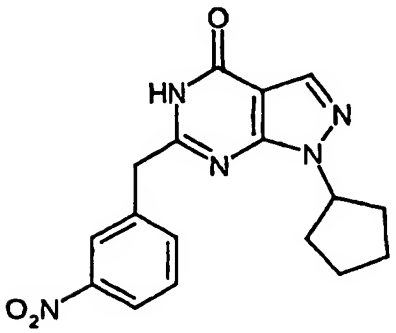
1-(1-Ethylpropyl)-6 -[3-(trifluoromethyl)benzyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 150 mg (0.75 mmol) of 5-amino-1-(1-ethylpropyl)-1H-pyrazole-4-carboxamide and 490 mg (2.25 mmol) of (3-trifluoromethylphenyl)-methyl acetate.
Yield: 159 mg (58% of th.)
MS (ESI): m/z = 365 $(M+H)^+$
mp.: 120°C
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.3 (s, 1H), 8.0 (s, 1H), 7.7 (s, 1H), 7.7-7.5 (m, 3H), 4.4 (m, 1H), 4.1 (s, 2H), 1.95-1.75 (m, 4H), 0.6 (t, 6H, J = 7.5 Hz) ppm.

Example 12

1-Cyclopentyl-6-(3-nitrobenzyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 668 mg (3.44 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 3.5 g (13.7 mmol) of (3-nitrophenyl)-ethyl acetate.

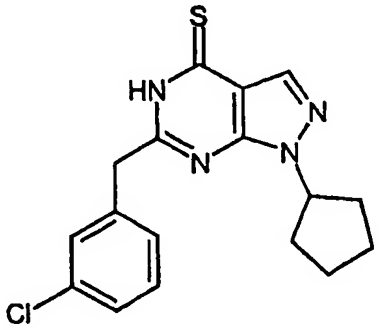
Yield: 10 mg (1% of th.)

MS (ESI): m/z = 340 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.3 (s, 1H), 8.3 (s, 1H), 8.15 (m, 1H), .8.0 (s, 1H), 7.8 (d, 1H, *J* = 8 Hz), 7.6 (t, 1H, *J* = 8 Hz), 5.0 (m, 1H), 4.15 (s, 2H), 2.1-1.6 (m, 8H).*

Example 13

6-(3-Chlorobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-thione



A solution of 50 mg (0.15 mmol) of 6-(3-chlorobenzyl)-1-cyclopentyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one (Example 1) in 1 mL of pyridine is reacted at room temperatiure with 50 mg (0.23 mmol, 1.5 equiv.) of diphosphorus pentasulfide and subsequently stirred overnight under reflux. After cooling, the reaction mixture is reacted with 10 mL of an ice-cold 2.5% solution of sodium hydrogen carbonate and extracted three times with ethyl acetate. The combined organic phases are washed with a saturated solution of sodium chloride, dried over sodium sulfate and evaporated under vacuum. The crude material is purified by preparative HPLC.

Yield: 36 mg (68% of th.).

MS (ESI): m/z = 345 $(M+H)^+$

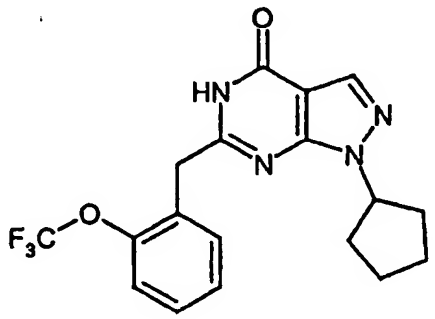
mp.: 154°C

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 13.6 (s, 1H), 8.15 (s, 1H), 7.5 (s, 1H), 7.4-7.25 (m, 3H), 5.05 (m, 1H), 4.1 (s, 2H) 2.1-1.6 (m, 8H).*

* "ppm" and m.p. temperature omitted in German original—*The Language Service.*
* "ppm" omitted – *The Language Service.*

Example 14

Cyclopentyl-6 -[2-(trifluoromethoxy)benzyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one



Analogously to Example 1, the product is obtained starting from 50 mg (0.26 mmol) of 5-amino-1-cyclopentyl-1H-pyrazole-4-carboxamide and 301 mg (1.29 mmol) of [2-(trifluoromethoxy)phenyl]methyl acetate.

Yield: 64 mg (63% of th.)

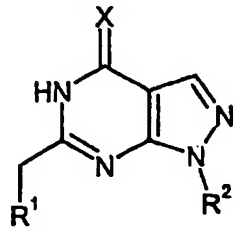
MS (DCI): m/z = 379 $(M+H)^+$

mp.: 161°C

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.25 (s, 1H), 8.0 (s, 1H), 7.5-7.3 (m, 4H), 4.9 (m, 1H), 4.1 (s, 2H),2.05-1.5 (m, 8H) ppm.

Patent claims

1. Compounds of the formula



(I),

in which

R^1 denotes phenyl that is substituted by 1 to 5 substituents selected independently of one another from the halogen, C_1-C_6 alkyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, nitro and C_1-C_6 alkoxy groups,

R^2 denotes pentane-3-yl, C_4-C_6 cycloalkyl,

X denotes oxygen or sulfur,

as well as their salts, solvates and/or solvates of these salts.

2. Compounds according to claim 1, in which

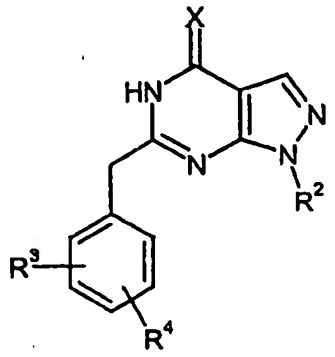
R^1 denotes phenyl that is substituted by 1 to 3 substituents selected independently of one another from the fluorine, chlorine. bromine, C_1-C_4 alkyl, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, nitro and C_1-C_4 alkoxy groups,

R^2 denotes pentane-3-yl, C_5-C_6 cycloalkyl,

X denotes oxygen or sulfur,

as well as their salts, solvates and/or solvates of these salts.

3. Compounds according to claims 1 and 2 of the formula



(Ia),

in which

R^3 denotes hydrogen or chlorine,

R^4 denoted fluorine, chlorine, bromine, methyl, trifluoromethyl,

R^2 denotes pentane-3-yl, cyclopentyl

X denotes oxygen or sulfur,

as well as their salts, solvates and/or solvates of these salts.

4. Compounds according to claims 1 through 3 of formula (Ia), in which

R^3 denotes hydrogen or chlorine,

R^4 denoted fluorine, chlorine, bromine, methyl, trifluoromethyl,

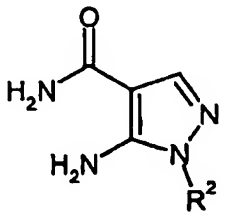
R^2 denotes pentane-3-yl, cyclopentyl

X denotes oxygen,

as well as their salts, solvates and/or solvates of these salts.

5. Method for the production of compounds according to claim 1, characterized in that

[A] Compounds of the formula



(II),

in which

R^2 has the meanings indicated in claim 1,

by reaction with a compound of the formula

$$R^1\text{-}CH_2\text{-}C(O)\text{-}Z \qquad \text{(IIIa)},$$

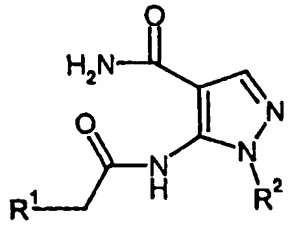
in which

R^1 has the meanings indicated in claim 1

and

Z denotes chlorine or bromine,

are converted in the presence of a base to compounds of the formula

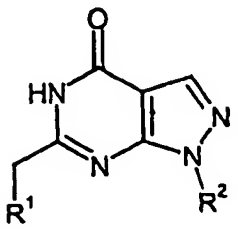


(IV),

in which

R^1 and R^2 have the meanings indicated in claim 1,

and then cyclized in the presence of a base to compounds of the formula



(Ib),

in which

R^1 and R^2 have the meanings indicated in claim 1,

or

[B] compounds of formula (II) are reacted under direct cyclization to (Ib) with a compound of the following formula

$$R^1\text{-}CH_2\text{-}C(O)\text{-}OR^5 \quad \text{(IIIb)}$$

in which

R^1 has the meanings indicated in claim 1

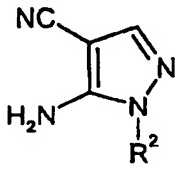
and

R^5 denotes methyl or ethyl,

in the presence of a base,

or

[C] compounds of the formula

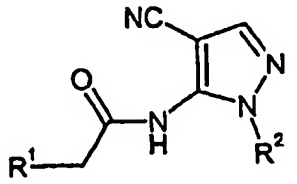


(V),

in which

R^2 has the meanings indicated in claim 1

are converted, first by conversion with a compound of formula (IIIa) in the presence of a base to compounds of the formula

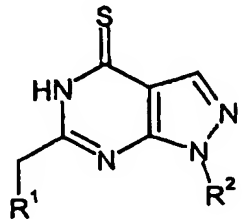

(VI),

in which

R^1 and R^2 have the meanings indicated in claim 1,

and these are cyclized, in a second step, in the presence of a base and an oxidation agent to (Ib),

and the compounds of formula (1b) are then optionally converted by reaction with a sulfuration agent, such as, for example, diphosphorus pentasulfide, to the thiono derivative of the following formula


(Ic),

in which

R^1 and R^2 have the meanings indicated in claim 1,

and the resulting compounds of formula (I) are converted to their solvates, salts and/or solvates of these salts optionally with the corresponding (i) solvents and/or (ii) bases or acids.

6. Compounds according to one of the claims 1 through 4 for the treatment and/or prophylaxis of disease.

7. Drugs containing at least one of the compounds according to one of the claims 1 through 4 and at least one pharmaceutically compatible, essentially nontoxic carrier or excipient.

8. Use of the compounds according to one of the claims 1 through 4 for the production of a drug for the prophylaxis and/or treatment of disorders of cognition, concentration, learning and/or memory.

9. Use according to claim 8, with the disorder being a consequence of Alzheimer's disease.

10. Use of the compounds according to one of the claims 1 through 4 for the production of a drug to improve cognition, concentration, learning and/or memory.

11. Method for combatting disorders of cognition, concentration, learning and/or memory in humans and animals by the administration of an effective amount of the compounds of claims 1 through 4.

12. Method according to claim 11, with the disorder being a consequence of Alzheimer's disease.